Infectious Diseases

Gilead's curative but high-priced hepatitis C pill Sovaldi stirred payer frustration after its launch smashed sales records. Now firms from biotech to big pharma are gunning for their share of the HCV business. Will cost competition come to this space and allow these would-be rivals to chip away at Gilead's dominance? **Noah Pines** reports from ringside

"Unprecedented" is the only way to describe the clinical advancement and the commercial, economic and governmental phenomena taking place in the hyper-dynamic hepatitis C (HCV) marketplace. These may be some of the biggest-selling drugs ever launched—with market estimates in the $20-billion range—and could be one of the fastest victories of pharmaceutical science over a viral disease that causes substantial morbidity and mortality.

Gilead Sciences' Sovaldi (sofosbuvir) made pharmaceutical sales history by chalking up a record-smashing $2.2 billion in its first full quarter (vs. consensus forecasts of $937 million-$1.1 billion).

The first among a breakthrough breed of HCV-battling nuc polymerase inhibitor anti-virals that when combined with other medicines will offer near certainty of clearing patients of the virus, Sovaldi set a new bar. "It's the most stellar launch we've ever seen," notes Julie Hoggatt, senior consultant for *in*Thought Research, a Symphony Health Solutions company.

To put that Q1 figure into perspective, the previous fastest-to-become-a-blockbuster was Vertex Pharmaceuticals HCV protease inhibitor Incivek/Incivo (telaprevir), which topped $1.5 billion in sales after a year. By offering greater effectiveness, tolerability and convenience, Sovaldi, as well as Johnson & Johnson's NS3/4A protease inhibitor Olysio (simeprevir), have rapidly replaced Incivek and Merck's PI, Victrelis (boceprevir).

Given the size of the treatment population in the US (3-4 million) and worldwide (about 170 million), and the fact that previous HCV treatment had tolerability snags, ISI Group's Mark Schoenebaum projects that Sovaldi could garner $8 billion or more this year and, ultimately, dethrone Pfizer's Lipitor as the top-selling drug of all time.

But the company faces formidable headwinds. The first is payer outcry over Sovaldi's price, a controversy that has reached from the US Congress to foreign governments such as India and Egypt; and the fact that there are several other competitors poised to launch equally effective competitive regimens later this year and into 2015, the most imminent being AbbVie's "3D" regimen.

The most vocal scorn over Sovaldi's $84,000-per-cycle US price has come from Express Scripts, the nation's largest PBM. It tried to enlist a coalition to boycott Sovaldi once new HCV regimens become available, claiming that the cost could bankrupt the national healthcare budget. Other insurers and ex-US health systems have weighed whether to limit usage only to the sickest patients.

Sovaldi's price also has caught the attention of House Democrat heavyweights, including Henry Waxman, who called Gilead to the carpet to justify Sovaldi's cost, especially given the high exposure that many state-run Medicaid programs face in covering the drug.

Ironically, there have been efforts to thwart Sovaldi's patent on the grounds of its lacking innovation. Patient advocates such as the legal-scientific coalition Initiative for Medicines, Access & Knowledge (I-MAK) and the charity Médecins Sans Frontières have called for dramatically lower-priced therapies, given that developing countries facing high HCV prevalence will not be able to afford its high cost.

TOP 25 INFECTIOUS DISEASES PRODUCTS, 2013

Category leaders, ranked by US sales, and their media spend

Rank	Product	Manufacturer	US sales $ (millions)	Vs. prior 12 months	TRx (000s)	Vs. prior 12 months	US DTC media $ (000s)	Vs. prior 12 months	US journal media $ (000s)	Vs. prior 12 months
1	**Atripla**	BMS/Gilead	$2,886.6	3.1%	1,208.0	-6.1%	$160.3	-80.0%	$334.0	-66.8%
2	**Truvada**	Gilead	$2,257.9	0.8%	1,521.0	-3.4%	$57.0	>100.0%	$227.0	>100.0%
3	**Rebif**	EMD Serono/Pfizer	$1,273.8	3.9%	252.0	-18.2%	$46.3	>100.0%	$0.0	-100.0%
4	**Avonex**	Biogen Idec	$1,245.5	-25.2%	238.0	-32.8%	$214.5	-38.4%	$900.0	-16.8%
5	**Isentress**	Merck	$1,023.2	10.8%	777.0	4.0%	$290.3	5.0%	$531.0	>100.0%
6	**Doxycycline HYCLAT**	Generic	$1,010.9	>100.0%	13,287.0	-14.5%	$0.0	N/A	$0.0	0.0%
7	**Prezista**	Johnson & Johnson	$999.8	21.7%	725.0	14.5%	$308.5	N/A	$1,296.0	76.2%
8	**Reyataz**	Bristol-Myers Squibb	$941.3	-1.1%	694.0	-8.6%	$145.5	-75.1%	$654.0	-20.6%
9	**Betaseron**	Bayer HealthCare	$812.6	1.1%	149.0	-16.3%	$0.0	N/A	$0.0	-100.0%
10	**Prevnar 13**	Pfizer	$809.2	3.7%	7.0	>100.0%	$1.5	-98.8%	$133.0	-90.0%
11	**Avonex Pen**	Biogen Idec	$771.2	>100.0%	145.0	>100.0%	$0.0	N/A	$0.0	0.0%
12	**Zyvox**	Pfizer	$728.8	2.1%	195.0	-6.3%	$0.0	N/A	$733.0	-11.5%
13	**Zostavax**	Merck	$705.9	7.7%	2,308.0	0.7%	$51,157.1	11.1%	$0.0	-100.0%
14	**Incivek**	Vertex	$701.9	-48.4%	33.0	-54.2%	$0.0	N/A	$0.0	-100.0%
15	**Gardasil**	Merck	$676.0	15.7%	44.0	12.8%	$48,794.4	11.8%	$0.0	0.0%
16	**Tamiful**	Roche	$650.1	84.3%	5,319.0	60.4%	$50,482.5	57.0%	$0.0	-100.0%
17	**Cubicin**	Cubist	$632.2	3.9%	44.0	0.0%	$0.0	N/A	$762.0	16.2%
18	**Complera**	Gilead	$630.9	82.3%	270.0	69.8%	$1,036.5	39.0%	$1,449.0	-7.1%
19	**Stribild**	Gilead	$605.5	>100.0%	192.0	>100.0	$1,724.5	>100.0%	$1,462.0	>100.0%
20	**Viread**	Gilead	$603.7	13.3%	601.0	3.1%	$0.1	N/A	$674.0	>100.0%
21	**Epzicom**	ViiV Healthcare	$539.8	6.3%	427.0	-1.4%	$0.0	N/A	$679.0	N/A
22	**Varivax**	Merck	$497.6	-39.1%	24.0	41.2%	$0.0	N/A	$0.0	N/A
23	**Norvir**	AbbVie	$489.0	-3.2%	1,383.0	-1.2%	$0.0	N/A	$0.0	N/A
24	**Fluzone**	Sanofi Pasteur	$475.8	>100.0%	3,809.0	>100.0	$5,002.3	-74.4%	$221.0	-81.6%
25	**Pneumovax 23**	Merck	$473.0	6.3%	765.0	21.6%	$1.8	-99.3%	$180.0	-84.0%

Sources: Sales/TRx, IMS Health; DTC media spend, Nielsen; journals, Kantar Media.
Note: List includes products FDA indicates as approved for treating AIDS, hepatitis B/C and bacterial infections, as well as vaccines and other antivirals.

I-MAK pegs a truly affordable HCV regimen at less than $500.

Gilead has been working with physicians to buttress its pharmacoeconomic posture. During a Q1 investor meeting following the European liver meeting EASL, during which several HCV contenders reported their own clinical data, Gilead President John Milligan said, "The value of a cure [is] underestimated in terms of the overall advantage to the healthcare system."

While doctors recognize Sovaldi's high cost, they attribute the controversy to mushrooming demand. Notes Dr. Ian Frank, an infectious-disease expert from the University of Pennsylvania, "It is not necessarily that much more expensive to cure people with sofosbuvir and simeprevir than it was to treat with a protease inhibitor plus interferon and ribavirin. It is just that the demand has increased exponentially." During the first quarter, an estimated 30,000 patients received Sovaldi.

Dr. Jonathan Fenkel, a hepatologist and director of the Hepatitis C Center at Thomas Jefferson University Hospital, points out another unique circumstance that boosted Sovaldi's launch: "Many patients were waiting and anticipating the launch of sofosbuvir for the past year, creating pent-up demand."

Prescriptions are likely to slow in the third quarter, Fenkel says, in anticipation of the release of the next generation of all-oral treatment, expected to be available in the next six months.

To strengthen its position internationally, Gilead is in deliberations with India-based pharmaceutical companies about manufacturing Sovaldi and offering it to developing countries at approximately $2,000 per treatment course.

Gilead is responding to its mounting competition by grooming a successor: an HCV single-tablet regimen (STR) that combines Sovaldi with ledipasvir (LDV), an NS5a inhibitor. With the FDA's Breakthrough Therapy designation and a 2,000-patient Phase-III clinical program dubbed "ION" at its back, the HCV STR could debut in the latter part of the year.

Response rates in the 8- and 12-week arms evaluating the once-daily Sovaldi/ledipasvir combo pill without ribavirin ranged from 94% to 98%. "Gilead is likely to remain dominant because they will be offering the most convenient option and have studied it across a broad range of patient types," says *in*Thought's Hoggatt. "Plus, we envision that as competition intensifies, companies will work with managed care and start negotiating prices."

The first competition to Sovaldi will likely be AbbVie's 3D combination regimen. Like the Sovaldi/ledipasvir combo pill, 3D also received a Breakthrough Therapy designation and could be approved before the end of 2014. 3D combines ABT-450, boosted with ritonavir (an HIV protease inhibitor and pharmacokinetic enhancer), ombitasvir (ABT-267), and dasabuvir (ABT-333).

Analysts are upbeat on AbbVie's prospects, especially given data it recently presented on the seriously ill segment of patients. "During the latest European liver meeting, AbbVie has been focusing more on genotype 1, especially difficult-to-treat patients such as prior

CLINICAL CORNER

Among the important developments in HIV/AIDS over the past few years is the advent of treatment-as-prevention strategies. Last month's move by the CDC to recommend Gilead's Truvada for HIV prevention shows it's a strategy public health officials still take seriously.

Clinical research has shown that not only does keeping a patient's viral load undetectable reduce HIV transmission, but also that treating uninfected people can lower the risk of infection. This approach, called "pre-exposure prophylaxis" or "PrEP" involves treating healthy people who may be at high risk for contracting HIV.

Ian Frank

Thus far, Truvada (tenofovir plus emtracitabine) is the only therapeutic modality the FDA has approved for usage as PrEP. According to the results of the iPrEx clinical trial, daily use of Truvada affords 44% more protection among men who have sex with men (MSM).

One downside is that Truvada's effectiveness depends on consistent usage. That can be a challenge for an individual who is not sick, especially when taking that medication can require regular serologic testing (for kidney abnormalities)—and is costing them a copayment. Researchers are looking at long-acting drugs, which can be given at much less frequent intervals in the setting of PrEP. Topping the list is GSK744, being developed by ViiV Healthcare, which markets several other HIV treatments such as Tivicay (dolutegravir) and Epzicom (abacavir + lamivudine fixed dose combination).

"There is interest in these agents not just as therapeutics but also as PrEP," notes Dr. Ian Frank, an infectious-disease specialist at the University of Pennsylvania and director of the Clinical Therapeutics Program of the Penn Center for AIDS Research. "If you have a drug that you can give every month or less frequently, that is exciting."

GSK744 data presented at the recent AIDS meeting, the Conference on Retroviruses and Opportunistic Infections (CROI), are encouraging. Investigators showed 100% protection in an animal model.

Another study presented on GSK744 at CROI also is a harbinger of future HIV management strategies: using long-acting antiretroviral (ARV) medicines as maintenance therapy. Today, the most convenient ARV regimens must be given once daily. While relatively convenient, that isn't ideal for someone who needs to take medicine in perpetuity.

At the meeting, Dr. David Margolis, a professor of immunology at UNC Chapel Hill, presented data from the Long-Acting antiretroviral Treatment Enabling" or "LATTE" study. LATTE demonstrated that an oral combo of two agents, Johnson & Johnson's Edurant (rilpivirine) and GSK744, was at least as effective as a conventional dual NRTI backbone plus Bristol-Myers Squibb's Sustiva (efavirenz) at holding the virus to undetectable levels.

Having demonstrated the duo's effect in the setting of maintenance therapy, the next step will be to validate their usage as once-monthly injectables, in lieu of daily pills.

failures, those with cirrhosis and transplant," points out Hoggatt. "They also continue to highlight their safety data."

Like the Gilead regimen, AbbVie's 3D entrant appears effective, with demonstrated rates of HCV cure in the high 90% range. The main difference is convenience—Gilead's regimen is one pill once daily, plus or minus ribavirin. AbbVie's regimen requires two pills to be taken in the morning, plus another pill at night, plus or minus ribavirin. AbbVie has communicated that it is working on co-formulating parts of the regimen to reduce pill burden.

Plus, there are potential 3D interactions, says Fenkel, the Jefferson hepatologist. "3D still requires a thorough review of concomitant medications for potential drug-drug interactions."

Importantly, payers have signaled that they are not going to allow convenience to overshadow their HCV cost-reduction efforts. Given that a course entails only 12-24 weeks of therapy, they have publicly indicated a desire to see cost competition in this space.

Looking to join the fray are several other biopharma heavyweights assiduously preparing their entrants to cross from clinic to pharmacy. Bristol-Myers Squibb recently joined the growing Breakthrough Therapy HCV club for its investigational dual regimen of daclatasvir (an NS5A inhibitor) and asunaprevir (an NS3 protease inhibitor) in patients with genotype 1b. The company has made Japan its commercial focus, since about three-quarters of the 1.2 million HCV infected individuals there have genotype 1b.

Merck unveiled robust Phase-II data for its HCV regimen at EASL, setting the stage for Phase-III trials by the end of 2014. Data presented at the London-based conference showed a near-perfect (98%) rate of cure in genotype-1 patients receiving the investigational duo of MK-5172 and MK-8742. Like Gilead's SOF/LDV, -5172 and -8742 have co-formulation potential and can be taken once daily.

Smaller biopharmas, like Cambridge, MA-based Idenix Pharmaceuticals, are gunning for their share of the HCV business. With nuc polymerase prodrug and NS5a candidates in Phase II, Idenix is sporting an all-oral, pan-genotypic, nuc-based cocktail. "We believe this regimen has the potential to play a significant role in advancing HCV care," points out Idenix CEO Ron Renaud.

In the world of HIV, aside from Truvada's prophylaxis recommendation from the CDC, an important entrant is expected to be ViiV's one-pill combination of Tivicay and Epzicom. Dubbed "Trii" and anticipated for a summer debut, it has drawn enthusiasm from HIV-treating providers since it is the first integrase combination pill that does not require a pharmacokinetic booster. The main potential challenge it may face is questions about one component of the regimen, abacavir, which has been associated with cardiovascular disease.

"Providers are using Tivicay; it is clearly a potent drug," notes UPenn's Frank. "The suite of studies in comparison to [Merck's] raltegravir and [BMS's] efavirenz, as well as [Johnson & Johnson's] boosted darunavir, are impressive. Tivicay is at least non-inferior, and in some cases superior to all of these products that are among the preferred agents in all treatment guidelines. The issues that that drug will face are issues with using abacavir."

Trii is expected to compete against Gilead's fixed-dose combination anti-viral brands, Stribild especially, which is expected to be upgraded with a new version of tenofovir, called tenofovir alafenamide.

There are likely to continue to be plenty of new patients for Gilead and ViiV to spar over. Despite vigorous prevention education in the 30 years since its discovery, the CDC reckons that there are still 50,000 new cases of HIV diagnosed in the US annually. ■